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Practice Patterns and Survival Outcomes of Intracranial Germinoma: An Analysis of the National Cancer Database

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Abstract

The goal of the study is to examine the practice pattern and survival outcome of adult and pediatric patients with intracranial germinoma. Patients from the National Cancer Database (NCDB) brain tumor registry between the years 2004–2014 with intracranial germinoma were extracted for analysis. Patients who had distant metastasis, received no treatments, or only surgery/chemotherapy alone were excluded. An age cutoff of >21 years old was used to define the pediatric population. Patients were stratified by the treatments radiation therapy alone (RT) and chemotherapy followed by radiation therapy (C+RT). 445 patients with intracranial germinoma meeting our inclusion criteria were identified. Of the adult patients, 65.7% received RT and 34.3% received C+RT, compared to the pediatric patients, where 31.8% received RT and 68.2% received C+RT. Those patients who received C+RT had a lower radiation dose compared to the RT group ($p < 0.001$). The 5 and 10 year overall survival (OS) for the entire cohort was 92.6% and 87.9%, respectively. Univariate analysis demonstrated improved OS with younger age, private insurance, C+RT treatment, and pediatric patients. Only age and insurance type remained significant on multivariate analysis. The 5 year OS was 92.6% (RT) vs 97.2% (C+RT) ($p = 0.307$) and 83.4% (RT) vs 95.4% (C+RT) ($p = 0.122$) in the pediatric and adult patients, respectively. There is a higher use of C+RT with an accompanied reduction in RT dose in the treatment of intracranial germinoma. There is no difference in survival between the treatment approaches of RT or C+RT in the NCDB patient cohort.

Keywords

intracranial germinoma; NCDB; chemotherapy; radiation therapy

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Compliance with ethical standards

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Formal consent

For this type of study formal consent is not required.

Introduction

Intracranial germ cell tumors have traditionally been a rare tumor with an estimated incidence of 0.20/100,000 person-years[1]. Intracranial germ cell tumors are further broken down into germinomatous and non germinomatous germ cell tumors with about 66%–75% of all cases being germinomas. Germinomas have classically been responsive to radiation therapy and patients with this diagnosis have an excellent prognosis[2]. The radiation therapy given were traditionally large field cranial spinal irradiation yielding excellent results [3]. However, given the excellent prognosis, the potential for late toxicities becomes critical in these long term survivors. Due to the rare nature of disease, management of the disease have been dictated largely by small prospective/retrospective data. The largest review of such has shown that it is likely safe to treat localized germinoma with limit cranial fields as opposed to extended fields [4].

Chemotherapy has gained prominence in the treatment of germinoma in recent years. Chemotherapy alone has been tried in the past. Results from that approach appear to be more limited due to the higher number of recurrences, although most recurrences were then subsequently salvaged [5], [6]. Another approach that has gained popularity recently is the addition of chemotherapy with subsequent reduction in radiation therapy dose. This allows for a possible decrease in neurocognitive and endocrine toxicities associated with radiation therapy [7]–[10]. Studies evaluating the combination of neoadjuvant chemotherapy followed by RT were completed with good results by the Pediatric Oncology Group (POG) and the International Society of Paediatric Oncology (SIOP)[11], [12], thereby, providing the rationale for the currently accruing protocol by the Children Oncology Group (COG) ACNS 1123 that examines radiation therapy dose reduction[13]. Since this remains a rare disease entity, direct comparison of multiple treatment regimens is likely not feasible. The goal of our study is to examine the current practice patterns for the treatment of germinoma in the United States and determine survival outcomes between radiation therapy alone (RT) and chemotherapy followed by radiation therapy (C+RT).

Methods

The National Cancer Database (NCDB), maintained by the American College of Surgeons and the American Cancer Society, was utilized for this research. The database represents more than 70% of newly diagnosed cancer cases in the United States.

We examined patients of all ages who received a diagnosis of intracranial germinoma from 2004–2014 in the database. Patients with metastatic disease, treatment with surgery or chemotherapy alone, chemotherapy after RT, no treatments, or empty treatment data were excluded from the analysis. Demographic data were included in the analysis (age, sex, race, insurance type, median income of home zip code, tumor size, total RT dose, RT technique, Charlson-Deyo score, hospital type, residence to treatment facility, and year of diagnosis). Multiple initial tumor data were excluded from statistical analysis due to incomplete data.

Statistical analysis was conducted using SPSS 24. Baseline patient characteristics were compared using either independent sample T-tests or chi square. The patients were stratified

into pediatric vs adult (age 21 as cutoff for pediatric patients). They were then further stratified to treatment of RT or C+RT. Kaplan-Meier survival estimates (log-rank test) were created based on the stratified groups. Univariate analyses (UVA) using cox regression were used to investigate for variables significantly correlated with overall survival. Variables that were significant on UVA were then tested with multivariate analysis (MVA) on overall survival (OS).

Results

208,559 patients were within the brain tumor database and 576 patients had the diagnosis of intracranial germinoma. A total of 445 patients fitting the criteria described above were available for analysis. 187 patients underwent RT and 258 patients underwent C+RT. Of the adult patients, 65.7% received RT and 34.3% received C+RT, compared to the pediatric patients, where 31.8% received RT and 68.2% received C+RT. The patient characteristics are shown in Table 1 by treatment group. The median follow up time was 58 months. There was a predominance of males (67.2%) with the diagnosis consistent with prior reports [1]. Black race and those with uninsured or unknown insurance were more likely to receive RT alone ($p=0.015$ and $p<0.001$ respectively). The median radiation dose for RT was 4500 cGy and 3600 cGy for C+RT, respectively ($p<0.001$). C+RT patients were more likely to receive intensity modulated radiation therapy (IMRT). Cut point analysis showed no significant trends in the use of RT vs C+RT over the years. The vast majority of the patients had a Charlson/Deyo score of 0. This score classifies comorbidity based on extracted International Classification of Disease (ICD) codes of specified conditions. A score of 0 suggests no comorbidity at the time of diagnosis. When examining the type of radiation treatment field received by patients, <1% of patients got an additional spine field.

Univariate analysis on overall survival for the entire cohort showed age as the strongest predictor for OS (HR 1.094 95% CI 1.062–1.127 $p<0.001$) with young patients doing better. Those with private insurance compared to government insurance also predicted for OS (HR 2.980 95% CI 1.283–6.919 $p<0.011$). In addition, age group and treatment received (RT vs C+RT) was also significant on UVA (Table 2). On MVA (Table 3), age remained the strongest predictor for OS (HR 1.084 95% CI 1.062–1.127 $p<0.001$). The insurance type also remained significant for OS (HR 3.109 95% CI 1.243–7.779 $p<0.015$) where those with government insurance have a three times increased risk of death compared to those with private insurance. The age group (adult vs. pediatric) and treatment type received were no longer significant on MVA, likely due to confounding effect by age, although a trend towards significance still remained ($p=0.055$ and $p=0.062$, respectively).

Kaplan-Meier survival curve were generated for the cohort. The 5 and 10 year overall survival (OS) for the entire cohort was 92.6% and 87.9%, respectively (Figure 1). For the adult patients, the 5 and 10 year OS was 83.4% and 78.8% in the RT group and 95.4% and 79.5% in the C+RT group respectively ($p=0.122$). For the pediatric patients, the 5 and 10 year OS was 92.6 and 92.6% in the RT group and 97.2 and 95.7% in the C+RT group respectively ($p=0.307$) (Figure 2).

Discussion

Our analysis of the NCDB showed that certain factors may predict whether a patient receives RT or C+RT. There is a predominance of C+RT used in the pediatric population. Whereas in adult patients, the RT alone is most often utilized. In addition, there was on average a radiation dose reduction for those patient who received chemotherapy (median 45Gy vs 36Gy). This is likely due to the hope to reduce radiation therapy related neurocognitive and endocrine effects. In addition, black race and those who are uninsured or with unknown insurance have a tendency to receive RT alone. This may in part be due to underlying socioeconomic factors. For our survival analysis, age was the strongest predictor of outcome with younger patients performing better than older patients. Although there was significance for the treatment type received (RT vs C+RT) on UVA, that significance was no longer present on MVA. This is likely due to the association of younger patients have more of a tendency to receive C+RT and with age as a confounding prognostic factor. Examining the Kaplan-Meier survival curves with stratification of treatment type, there was no difference in survival between the treatment modalities in both adults and pediatric populations. Again, pediatric patients performed better with better 10 year survival around 94% compared to 79% for the adult patients.

Our results are important due to the large number of patients used in the analysis from the NCDB database to examine the question of treatment type in this rare tumor. Our RT alone data is consistent with multiple prior publications in terms of survival. The 2 larger series from MAKEI and Japan both had 10 year survival of 93.7% and 90% respectively[3], [14]. In addition, our results show that practitioners are no longer using large CSI fields for treatment with <1% of the patients receiving a spine field. The study publish by Rogers et al. demonstrated that reduced-volume irradiation is safe and with the potential benefit of decreasing toxicity[4]. The NCDB database is limited in that it is not able to specify the specific cranial RT received by the patient (whole ventricle radiation therapy + boost versus focal radiation therapy only). The patients in the C+RT group were more likely to receive IMRT in this cohort. There have been dosimetric studies that demonstrate improvement of IMRT when compared to conventional treatment[15]. With the emergence of proton therapy, there have also been dosimetric advantages shown with the modality[16]. In addition, there have been studies that demonstrate use of IMRT and proton therapy may be able to prevent the decline of intelligence quotient in pediatric patients[17], [18].

The use of C+RT, which allows for a RT dose reduction, has gained prominence in the recent years due to the potential for neurocognitive and endocrine toxicities associated with radiation therapy, which is particularly relevant in the pediatric population [7]–[10]. POG 9530 prospectively examined C+RT use in 12 germinoma patients. The radiation dose was dependent on the response to chemotherapy in that protocol. The outcomes appeared comparable to RT alone in this small prospective series[11]. A retrospective series of 81 patients from Korea compared the use of RT vs C+RT. They showed a worse recurrence free survival with the use of C+RT vs RT (88.1% vs 100% $p=0.0279$). There was no difference in their survival outcomes. They did also show a decrease in hormonal replacement with the use of C+RT in their cohort [19]. The largest prospective non randomized cohort comparing RT vs C+RT was from the SIOP CNS GCT 96 study. Their study showed that for localized

disease, 5 year progression free survival was significantly better for the RT (CSI) group (97% vs 88% $p=0.04$). There was again no difference in survival[12]. Based on those studies, there may be slightly worse recurrence rates with C+RT approach without a difference in survival. Unfortunately, no relapse data are present in NCDB but our survival data are consistent with the above and showed no survival difference. The COG ACNS 1123 will be examining germinoma patients who will undergo neoadjuvant carboplatin and etoposide for 4 cycles. Those with a partial or complete response will then receive 18Gy to the whole ventricle followed by 12Gy boost to the involved brain[13]. The dose will be a significantly lower dose than the previous reports (40–56Gy dose range) and our study (median 36Gy) and the results are pending at this time.

Those with private insurance also had improved OS of MVA and again likely represent the effect of underlying socioeconomic factors. Multiple prior studies on different childhood malignancies have shown different socioeconomic factors such as race, education level, and income having an effect on survival and other cancer outcomes [20]–[22]. Race, income, distance from facility, and treatment center did not have an impact on survival in the current study. The only socioeconomic factor that was significant from our analysis was government insurance type. There have been specific studies on insurance type and survival outcome. In a recent publication examining 8219 pediatric cancer patients (age <15 years old), Medicaid insurance patients did not have any difference in survival compared to those with private insurance[23]. Similar publications examining insurance type in the young adult (age 15 years old) cancer patient population have shown those with Medicaid insurance showed an association with increased risk of death[24], [25]. However, this topic remains complex and no single factor is likely the cause for inferior outcomes in patients with lower socioeconomic status.

The limitations of our study are typical of NCDB analysis with possibility of unknown covariates not documented influencing our results. In addition, the type of chemotherapy was not documented well with regards to the specific agents and number of cycles given. The sequencing of chemotherapy and radiation therapy was inferred from the start date of treatment. Also, multiple tumor characteristics had limited data such as location, laterality, and focality etc. There was also no beta-HCG or alpha fetoprotein data. Fortunately, the prognosis of germinoma is excellent and not dependent on many of those factors and the missing data should not significantly confound the survival data. Finally, toxicity data is not available for these patients.

A potential avenue for improving results in these patients may be public health and social policy that may provide an even more dramatic improvement in outcomes. What will be important in determining the optimal treatment approach will ultimately be the toxicity of treatments. To our knowledge, this is the largest analysis of the use of RT vs C+RT for patients with intracranial germinoma. This will add evidence to support the use of both treatment modalities. Future prospective data with focus on toxicity will be important to further elucidate the benefit of C+RT.

In conclusion, our study showed age and insurance type as a significant factor in survival and support the use of both RT and C+RT in terms of survival for the treatment of germinoma.

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Fig. 1.
Overall survival of adult patients stratified by RT vs C+RT (p=0.122)

Fig. 2.
Overall survival of pediatric patients stratified by RT vs C+RT ($p=0.307$)

Table 1.

Patient Characteristics by RT alone vs. Chemo followed by RT (n=445)

	RT Alone N=187	Chemo followed by RT N=258	P
Age (years)	21 (median)	15 (median)	<0.001
Gender			0.095
Male	133 (71.1%)	164 (63.6%)	
Female	54 (28.9%)	94 (36.4%)	
Race			
White	136 (72.7%)	197 (76.4%)	0.384
Black	29 (15.5%)	21 (8.1%)	0.015
Other	22 (11.8%)	40 (15.5%)	0.262
Insurance			
Private	107 (57.2%)	159 (61.6%)	0.347
Government	48 (25.7%)	76 (29.5%)	0.379
Uninsured/Unknown	32 (17.1%)	23 (8.9%)	<0.001
Income			0.895
<\$30000	22 (11.8%)	25 (9.7%)	
\$30000-\$34999	32 (17.1%)	46 (17.8%)	
\$35000-\$45999	51 (27.3%)	73 (28.3%)	
\$46000+	76 (40.6%)	98 (38%)	
Follow-up Time (months)	56 (median)	54 (median)	0.520
Tumor size (mm)	27 (median)	30 (median)	0.132
RT Total Dose (Gy)	45 (median)	36 (median)	<0.001
RT Technique			
EBRT/3D-CRT	134 (71.7%)	152 (58.9%)	0.006
IMRT	41 (21.9%)	83 (32.2%)	0.017
Proton	4 (2.1%)	15 (5.8%)	0.056
Not Specified	8 (4.3%)	8 (3.1%)	0.503
Age Group			<0.001
Adult	88 (47.1%)	46 (17.8%)	
Ped	99 (52.9%)	212 (82.2%)	
Charlson/Deyo Score 0 1 2			0.557
0	176 (94.1%)	238 (92.2%)	
1	10 (5.3%)	16 (6.2%)	
2	1 (0.5%)	4 (1.6%)	
Hospital Type			0.178
Urban/Other	31 (16.6%)	56 (21.7%)	

	RT Alone N=187	Chemo followed by RT N=258	P
Metro	156 (83.4%)	202 (78.3%)	
Residence to treatment facility			0.436
<20 miles	94 (50.3%)	134 (54%)	
>=20 miles	93 (49.7%)	114 (46%)	
Years of initial diagnosis			
2004	17 (9.1%)	15 (5.8%)	
2005	8 (4.3%)	25 (9.7%)	
2006	16 (8.6%)	23 (8.9%)	
2007	23 (12.3%)	26 (10.1%)	
2008	26 (13.9%)	13 (5%)	
2009	13 (7%)	23 (8.9%)	
2010	21 (11.2%)	33 (12.8%)	
2011	21 (11.2%)	25 (9.7%)	
2012	7 (3.7%)	24 (9.3%)	
2013	15 (8%)	24 (9.3%)	
2014	20 (10.7%)	27 (10.5%)	

Table 2.

UVA for OS

	P	HR (95%CI)
Age	<i><0.001</i>	1.094 (1.062–1.127)
Gender		
Female vs. Male	0.702	0.849 (0.366–1.967)
Race		
Black vs. White	0.705	1.232 (0.419–3.624)
Other vs. White	0.503	0.608 (0.141–2.612)
Insurance		
Government vs. Private	<i>0.011</i>	2.980 (1.283–6.919)
Uninsured/Unknown vs. Private	0.424	1.692 (0.465–6.165)
Income		
\$30000-\$34999 vs. <\$30000	0.697	1.243 (0.416–3.710)
\$35000-\$45999 vs. <\$30000	0.385	0.590 (0.179–1.940)
\$46000+ vs. <\$30000	0.231	0.467 (0.134–1.622)
Tumor size	0.250	1.012 (0.922–1.032)
RT Technique		
IMRT vs EBRT/3D-CRT	0.276	0.549 (0.186–1.615)
Age Group		
Ped vs Adult	<i>0.003</i>	0.291 (0.131–0.648)
Charlson/Deyo Score		
1 vs. 0	0.496	1.653 (0.389–7.014)
2 vs. 0	0.979	N/A (small n)
Treatment		
Chemo+RT vs. RT Alone	<i>0.015</i>	0.315 (0.151–0.813)
Hospital Type		
Metro vs. Urban/Other	0.185	2.661 (0.627–11.295)

Table 3.

MVA for OS

	P	HZ (95%CI)
Age	<i><0.001</i>	1.084 (1.062-1.127)
Insurance		
Government vs. Private	<i>0.015</i>	3.109 (1.243-7.779)
Uninsured/Unknown vs. Private	0.276	2.109 (0.5518.074)
Age Group		
Ped vs Adult	0.055	0.419 (0.172-1.020)
Treatment		
Chemo+RT vs. RT Alone	0.062	0.384(0.140–1.051)